In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 12-477V

Filed: September 8, 2016

K.T., a minor, by her mother and natural guardian, ALISHA DUDENHOEFFER,	*	**TO BE PUBLISHED**
Petitioners,	*	Special Master Hamilton-Fieldman
v.	*	Vaccine Act Entitlement; Causation-in-Fact; Measles-Mumps-Rubella ("MMR") Vaccine; Myclonic-Astatic Epilepsy ("MAE"); Epileptic Encephalopathy ("EE"); Molecular Mimicry.
SECRETARY OF HEALTH AND HUMAN SERVICES	*	
Respondent.	*	

Clifford John Shoemaker, Shoemaker and Associates, Vienna, VA, for Petitioner.
Darryl R. Wishard, United States Department of Justice, Washington, DC, for Respondent.

DECISION[1]

Alisha Dudenhoeffer ("Petitioner"), on behalf of her daughter, K.T., petitions for compensation under the National Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-1 to -34 (2012) (hereinafter "Vaccine Act"). Petitioner alleges that K.T. developed Myoclonic-Astatic Epilepsy ("MAE") (also known as "Doose Syndrome") as a result of the administration of the

[1] Because this decision contains a reasoned explanation for the undersigned's action in this case, the undersigned intends to post this decision on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 (2012). Each party has 14 days to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b).

Measles-Mumps-Rubella ("MMR") vaccine on August 6, 2009. For the reasons set forth below, the undersigned concludes that Petitioner has not met her burden of proof under the Vaccine Act, as delineated in *Althen v. Sec'y of HHS*, 418 F.3d 1274 (Fed. Cir. 2005), and therefore dismisses the petition.

I. Factual Background

On August 1, 2008, K.T. was born. Pet'r's Ex. 7 at 7.[2] Over the next seven months, K.T. developed normally, albeit undergoing several bouts with sinus-, digestive-, and allergy-related issues. *See* Pet'r's Ex. 15 at 111-23. During this time period, K.T. received her initial dose of the Hepatitis B vaccine, as well as all three doses of the Hib, Pediarix, Prevnar, and Rotateq vaccines, with no noted side effects. *Id.*

On April 13, 2009, an ambulance transported K.T. to the hospital for a seizure. Pet'r's Ex. 3 at 4, ECF No. 9-4. K.T.'s father recalled that she had been shaking and coughing in the middle of the night. Pet'r's Ex. 7 at 109. He explained that he watched her for a minute, until she went limp, at which point he picked her up and called the ambulance. *Id.* The attending physician at the emergency room noted that K.T. had no similar episodes in the past; but, K.T. had been sick for the previous two days with a fever and runny nose, and had a rash on her leg for the past two months. *Id.* at 109-10. The physician also reported that there was a strong smell of gas in the house when the ambulance arrived, yet no other household members had symptoms worthy of note. *Id.* Ultimately, the physician diagnosed K.T. with a febrile seizure. *Id.* at 110.

Four days later, on April 17, K.T. attended a follow-up appointment, where the physician observed that K.T.'s condition had improved and that she had suffered no subsequent seizure-like activity. Pet'r's Ex. 9 at 123. The doctor again diagnosed K.T. with a febrile seizure, and instructed her parents to discontinue her formula, in the hopes of improving a rash. *Id.*

Between then and August 6, K.T. started drinking different formula, *id.* at 122, and suffered from a febrile urinary tract infection, *see* Pet'r's Ex. 11 at 44-45, ECF No. 14-3, but otherwise did not seek medical attention. On June 11, K.T. appeared normal at a routine check-up with Dr. Susan Voss, her pediatrician. Pet'r's Ex. 9 at 122.

She again appeared normal at another routine check-up with Dr. Voss on August 6, 2009. Pet'r's Ex. 15 at 100. There, she received her Hepatitis A and MMR vaccinations, the latter of which forms the basis for her claim, and her fourth Prevnar vaccination. *Id.*

[2] The undersigned provides no ECF number for documents filed via compact disc.

Three days later, on August 9, K.T. began to suffer from a cough and a fever. Pet'r's Ex. 6 at 16, ECF No. 9-8. Two days thereafter, K.T. visited a medical clinic, where the nurse noted that she received the aforementioned shots, was exposed to thrush and the flu, and exhibited a loss of appetite, fever, a sore throat, coughing, and diarrhea. *Id.* The nurse diagnosed her with a febrile seizure "secondary to immunizations," and explained that it was "ok" for K.T. to return to daycare. *Id.*

In an unsworn letter filed with the Court, K.T.'s daycare provider, Erin Lucero, attested to what followed:

> After [K.T.] received her immunizations I noticed a change in [K.T.]. She started staring off for a second or two as if she wasn't sure what was going on. If [K.T.] was walking around she would blink and it would throw her balance off, sometimes to the point she would fall. I called [Petitioner] in the morning and advised her that I felt something wasn't right. I advised her to call the doctor.

Pet'r's Ex. 14 at 1, ECF No. 15-2.

On August 18, 2009, K.T. traveled to the hospital, where Petitioner reported that, for the previous 24 hours, K.T. endured episodes in which she rolled her eyes, dropped her arms, and then became motionless and unresponsive. Pet'r's Ex. 7 at 196. These episodes had grown more frequent and lengthier on the morning of the visit. *Id.* Petitioner also informed the treating physician that K.T. recently received the aforementioned immunizations and "developed a fever shortly after that" which "lasted intermittently for the next 5-6 days." *Id.* Petitioner further described K.T.'s "history of febrile seizure in April secondary to a urinary tract infection." *Id.*

On the same day, the treating physician transferred K.T. to another hospital "for further evaluation and management of episodes of unresponsiveness." Pet'r's Ex. 11 at 3, ECF No. 14-3. At that hospital, Petitioner relayed that K.T. "began having episodes of 'going blank' with her arms going limp to her sides for 5-15 seconds" once or twice per day from August 15 to 17. *Id.* On the eighteenth, K.T. suffered ten such episodes in a 20 minute window at daycare. *Id.* At the same time, Petitioner indicated, K.T. "snaps out of the episode quickly and acts normal afterwards" and was "active and healthy other than a fever for about a week after [her] immunizations." *Id.* Moreover, the treating physician noted, K.T. had "met all of her developmental milestones," was "cruising currently," and was "a very verbal child with good motor skills." *Id.* at 13. Notably, K.T.'s paternal grandmother reported that K.T.'s cousins "had seizures and take medicine for it." *Id.* at 4. In sum, the treating physician believed that K.T.'s "episodes of unresponsiveness . . . may be evidence of new onset seizure disorder," and ordered

an EEG, which "revealed abnormal spike and wave pattern at about 2-2.5 hz and was generalized in nature." *Id.* at 6, 18. As a result, the physician gave K.T. Keppra. *Id.* at 16.

The following day, K.T. underwent a sedated MRI, which revealed no abnormalities. *Id.* The treating physician discharged K.T. with a prescription for Keppra and ordered that she follow-up with a neurologist in two months. *Id.*at 16-18.

One week afterward, on September 3, 2009, Petitioner called Dr. Voss and reported that K.T. was "acting funny" following an unspecified procedure at the hospital. Pet'r's Ex. 9 at 121. Petitioner expressed frustration that K.T.'s episodes of unresponsiveness had not yet ceased. *Id.*

On October 6, Dr. Sergio Facchini, a neurologist, examined K.T. *Id.* at 110. He noted that K.T.'s episodes had continued since the August 18 hospital visit, often several times a day and as frequently as fifteen times in one day, despite her use of Keppra. *Id.* But he observed neither "loss of muscle tone" nor "postictal fatigue or sleep." *Id.* Overall, Dr. Facchini asserted, K.T. was a "healthy and neurologically-normal toddler" with "a history of . . . a single generalized tonic-clonic seizure with fever" and "episodes of being unresponsive for a few seconds." *Id.* at 111. Dr. Facchini ordered that K.T. undergo EEG telemetry to "determine the etiology of the episodes," and instructed Petitioner to gradually decrease K.T.'s dose of Keppra. *Id.*

Roughly one month later, on November 4, K.T. went to a clinic for congestion, coughing, teething, and decreased appetite. Pet'r's Ex. 6 at 15. Notably, Petitioner reported that K.T.'s episodes had increased in frequency and duration, occurring 20-40 times per day for 5-30 seconds each. *Id.*

On November 20, 2009, Petitioner telephoned the hospital, explaining that K.T. typically fell immediately following her episodes. Pet'r's Ex. 9 at 113. Three days later, K.T.'s EEG showed abnormalities, including (a) sharp waves in the right posterior temporal region, and right and left central regions, and (b) an axial tonic seizure in the right posterior temporal region. *Id.* at 44. K.T. restarted her prescription of Keppra, and two days later, Petitioner called the hospital and noted that K.T.'s seizures had decreased in frequency. *Id.* at 46, 54.

But on December 3, Petitioner telephoned Dr. Facchini to inform him that K.T.'s seizures were beginning to increase in frequency. *Id.* at 52-53. In turn, Dr. Facchini increased K.T.'s dose of Keppra. *Id.* at 52.

About two weeks later, on December 18, 2009, Dr. Facchini wrote Dr. Voss, documenting his observations:

> [K.T.] is a 16-month-old girl with a history of what appears to be myoclonic-astatic seizures documented on telemetry. . . . The seizures continue unabated [despite increasing doses of Keppra]. Previously the parents had told me that she never fell during the seizures. However, today they state that there ha[ve] been occasions where if she is walking she may fall down during a seizure. The seizures are described as a vacant stare, and cessation of activity. On telemetry it was also found that she had some head nodding consistent with myoclonic seizures. One possibility since she is neurologically intact and has been developing well and has a normal MRI is that she may have Benign Infantile Myoclonic Epilepsy.
>
> Another possibility, also because she has a normal MRI and normal development, is that she may have Doose syndrome, even though this would be a somewhat early onset for myoclonic-astatic seizures of childhood. The possibility of Dravet Syndrome is also a consideration. Her development continues to be normal in all areas. She is now speaking several words and making small sentences.

Id. at 47. Dr. Facchini, noting her failure to respond to Keppra, prescribed her Zonisamide and ordered that she return for a follow-up in three to four months, unless her seizures persisted after three to four weeks of consuming Zonisamide. *Id.* at 48.

On January 25, 2010, Petitioner telephoned Dr. Facchini to and let him know that K.T. was still suffering from seizures every fifteen minutes, albeit only for five to ten seconds. *Id.* at 52. Dr. Facchini increased K.T.'s dose of Zonisamide and requested that Petitioner attempt to videotape K.T.'s seizures, if at all possible. *Id.* at 51.

Roughly three weeks afterward, on February 16, Dr. Facchini examined K.T. again. *Id.* at 39. He noted that K.T.'s "parents think that the seizures improved somewhat with [Z]onisamide," and that "the majority of the myoclonic seizures [were] in the form of a subtle head drop without falls," but that she still fell "occasionally." *Id.* Ultimately, he concluded that K.T. had "[p]ossible Doose Syndrome (Myoclonic-Astatic Epilepsy)," which initially presented as "a generalized tonic-clonic seizure during a febrile illness." *Id.* at 53. He planned to increase K.T.'s dose of Zonisamide and start her on a ketogenic diet. *Id.* For the next seven months, K.T. was not seen for her seizures, although she did suffer the occasional sinus and digestive issues. *See* Pet'r's Ex. 15 at 56-69.

On September 29, 2010, K.T. visited Dr. Vincent Gibbons and Dr. David Walsh, two neurologists, for a second opinion regarding her condition, which Petitioner described as "head

drops since 1 year of age." Pet'r's Ex. 10 at 8, ECF No. 14-2. An EEG showed abnormalities in the form of "generalized or rapidly secondarily generalized sharp and slow waves suggestive of epilepsy." *Id.* at 9.

Two days later, on October 1, Dr. Walsh saw K.T. for seizure management. *Id.* at 11. He noted that K.T. suffered from numerous seizures and had "significant speech delay." *Id.* Although Petitioner understood K.T.'s speech and K.T. never underwent speech therapy, "others (including her grandmother) report only understanding 2-3 words of her speech." *Id.* Dr. Walsh diagnosed her with "atonic seizures with poor control on Zonisamide and speech delay." *Id.* at 12. Heplanned to start her on Depakote, wean her off of Zonisamide, and refer her to an audiologist and a speech therapist. *Id.*

After months without any medical treatment (other than her Depakote prescription and the occasional sinus or stomach issue), K.T. returned to Dr. Walsh on July 8, 2011, and Petitioner indicated that K.T. was seizure free. *Id.* at 18. Petitioner felt that K.T. was "growing and developing well, except perhaps for her language." *Id.* Dr. Walsh noted no major medical developments or concerns, and specified that there was "[n]othing to suggest regression or loss of function." *Id.* That being said, Dr. Walsh observed that while "her language seemed fine, . . . her articulation was somewhat poor," although "nevertheless understandable." *Id.*

Six months thereafter, on January 4, 2012, K.T. again visited Dr. Walsh. *Id.* at 36. Petitioner reported "no seizures," and was "pleased to note that [K.T.'s] speech seem[ed] to be getting better." *Id.* Dr. Walsh made no changes to K.T.'s current regimen and ordered that they continue to schedule follow-up appointments every six months. *Id.*

At the next follow-up, on June 15, K.T. met with Dr. Gibbons. *Id.* at 37. Dr. Gibbons documented no major changes, except for continued problems with K.T.'s use of language:

> She continues to have very indistinct speech. [Petitioner] says that her hearing has been tested and found to be normal. She appears to understand speech appropriately, but has a difficult time with pronunciation, has developed some stuttering over the last several months, and has particular difficulty when she tries to speak quickly. There is also an element of orobuccal apraxia with coughing and choking on very thin liquids, such as tap water. Her expressive speech problems are static to perhaps improving slightly, and she has not shown any regression in other areas.
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> . . . She was alert and had moderately severe dysarthria and developmental diction difficulties. Her voice was also very loud and poorly modulated. . . .

> . . .
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> Her language difficulties appear to be with expressive speech, and she may very well have a speech apraxia in addition to an orobuccal apraxia. At this point, her language difficulties would certainly impact her learning ability, and I suggested to mother that she visit the neighborhood school and arrange for an evaluation through special school district, which in all likelihood will result in the finding of at least expressive language difficulties with a need for speech therapy that would hopefully begin in the fall.
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> . . . I suspect that the combination of this type of seizure problem, coupled with her expressive language difficulties means that she has a symptomatic epilepsy and is likely to hold onto her seizure tendency somewhat longer than a child who has an idiopathic seizure problem. . . .

Id. at 37-38. Given K.T.'s stable condition, Dr. Gibbons made no changes to her treatment regimen. *Id.* at 38.

On September 26, 2012, Dr. Voss penned a generally addressed letter opining that K.T. "had a febrile seizure after she received the MMR vaccine as a one year old." Pet'r's Ex. 12 at 1, ECF No. 14-4. Dr. Voss "recommend[ed] that she not receive further vaccines until her pediatric neurologist clear[ed] her for these vaccines." *Id.*

Five months later, on February 1, 2013, K.T. returned to Dr. Gibbons for a check-up. Pet'r's Ex. 37 at 6. Dr. Gibbons asserted that K.T. was still seizure-free and that she had "made tremendous improvement in her speech, and she [was] much more understandable," after undergoing speech therapy." *Id.* Dr. Gibbons also reported that Petitioner was "convinced that [K.T.'s] seizures were somehow the result of an immunization she received at her 1 year visit to the pediatrician , but without first-hand data from the time period surrounding her first event, it is impossible for us to corroborate such relationship." *Id.* Going forward, Dr. Gibbons decided to continue Petitioner on the same regimen, ordered a follow-up in six months, and noted the following:

> Education: Given the typical age of onset or seizures generally occurring around the same age as childhood immunizations, it is difficult to identify [K.T.]'s vaccine as the likely cause of her epilepsy. Since we have no records from her initial presentation of seizure and we do not know the associated events, it is impossible for this office to affirm a medical contraindication for future

> immunizations. A more appropriate authority would be the physicians in charge of her care at the time of her first seizure presentation.
>
> Though [K.T.] has not experienced a seizure in over two years, her language delay produces some concern about attempting to taper her at this time. We should revisit the topic as she continues to improve in her speech and language skills.

Id. at 7.

Since that time, K.T. has seen Dr. Gibbons for several regular check-ups without incident. *Id.* at 24-28, 156-61, 172-73. K.T. continues to be seizure free and still takes Depakote. *Id.* at 172-73.

II. Procedural History

On July 27, 2012, Petitioner sought compensation under the Vaccine Act. Pet., ECF No. 1. She alleged that the administration of the MMR vaccine, on August 6, 2009, caused K.T. to develop epilepsy. Pet. at 3.

Subsequently,[3] Respondent argued that Petitioner was not entitled to compensation, as she had not shown, by a preponderance of the evidence, that the MMR vaccine caused K.T. to develop MAE. Resp't's Report at 11-17, ECF No. 32. At the outset, Respondent claimed, Petitioner failed to sufficiently establish the nature of K.T.'s alleged injury. *Id.* at 13. In any event, Petitioner offered neither a medical theory linking the MMR vaccine and chronic seizure disorders nor specific evidence demonstrating that K.T.'s seizures were the result of the vaccination. *Id.* at 13-16.

In response, Petitioner filed an expert report from Dr. Yuval Shafrir.[4] Pet'r's Ex. 16, ECF No. 35-2. Dr. Shafrir opined that K.T. developed MAE as a result of the administration of the MMR vaccine. *Id.* at 15.

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[3] Initially, this case was assigned to Special Master Lord before it was reassigned to Special Master Vowell, and ultimately, to the undersigned.

[4] Dr. Yuval Shafrir received his medical degree from Tel Aviv University in 1982; completed a pediatric neurology residency at Washington University in St. Louis, and a pediatric epilepsy and neurophysiology fellowship at Miami Children's Hospital; and served as associate professor at Georgetown University and the University of Oklahoma. Pet'r's Ex. 17 at 1-3, ECF No. 35-3; Tr. at 67. He is board-certified in clinical neurophysiology, and neurology with

Respondent countered with an expert report from Dr. Gregory Holmes.[5] Resp't's Ex. A, ECF No. 42-1. Dr. Holmes contended that K.T.'s seizure disorder was not related to the MMR vaccination, asserting that the onset of her condition occurred following a fever five months prior to the MMR vaccination. *Id.* at 4-5. Even if this seizure was unrelated to Petitioner's ultimate disorder, Dr. Holmes continued, there was no evidence to suggest a link between the MMR vaccination and seizures. *Id.* at 5-6.

Following a status report, Dr. Shafrir filed a supplemental expert report, contesting Dr. Holmes' positions that (1) K.T. had failed to articulate a clear diagnosis of K.T.'s injury and (2) there was no mechanism by which the MMR vaccine could cause MAE. Pet'r's Ex. 38 at 1-6, ECF No. 53-2. Dr. Holmes responded with a supplemental report of his own. Resp't's Ex. L, ECF No. 58-1.

On December 11, 2014, the undersigned presided over a hearing in Washington, DC, at which Petitioner, Dr. Shafrir, and Dr. Holmes testified. Tr. at 3. Following the hearing, both parties filed briefs summarizing their positions on entitlement. The matter is now ripe for determination.

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a special qualification in child neurology; he was board-certified in pediatrics, but did not renew his certification due to cost and time concerns. Pet'r's Ex. 17 at 2; Tr. at 67-68. Currently, Dr. Shafrir operates a private pediatric neurology practice in Baltimore, Maryland. Pet'r's Ex. 17 at 3; Tr. at 67. At the subsequent hearing, the undersigned admitted Dr. Shafrir as an expert in the field of pediatric neurology, epilepsy, and interpreting EEGs. Tr. at 68-70.

[5] Dr. Holmes received his medical degree from the University of Virginia in 1974 and completed residencies at Yale University in pediatrics and at the University of Virginia in pediatric neurology. Pet'r's Ex. B at 1, ECF No. 42-2; Tr. at 157. He is board-certified in pediatrics, clinical neurophysiology, and neurology (with special competence in pediatric neurology). Pet'r's Ex. B at 1; Tr. at 158. Presently, Dr. Holmes serves as the Chair of the Department of Neurological Sciences at the University of Vermont, College of Medicine, where he both teaches and treats patients. Pet'r's Ex. B at 2; Tr. at 158-59. At hearing, Dr. Holmes specified that he treated patients with epileptic seizures, epilepsy, epileptic encephalopathy ("EE"), and MAE. Tr. at 159. Moreover, Dr. Holmes indicated that the primary focus of his research was EE, on which he has published several articles and book chapters, and for which he has received awards from numerous organizations. *Id*. at 160. At the hearing, Dr. Holmes was admitted as an expert in the field of pediatric neurology. *Id*. at 161.

III. Analysis

A. Legal Standard

The Vaccine Act provides compensation for two types of injuries: "Table" and "Off-Table." *See* 42 U.S.C. § 300aa-11(c)(1)(C) (2012). To receive compensation for a "Table" injury, a petitioner must demonstrate that she received a vaccine and developed an injury in the manner specified by the Vaccine Injury Table. § 300aa-11(c)(1)(C)(i). Where, as here, a petitioner does not allege a "Table" injury, she must prove that a covered vaccine actually caused her "Off-Table" injury. § 300aa-11(c)(1)(C)(ii).

For a petitioner to prove that a covered vaccine actually caused her injury, she must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly v. Sec'y of HHS*, 592 F.3d 1315, 1321 (Fed. Cir. 2010) (internal quotation marks omitted). In *Althen*, the Federal Circuit delineated three prongs that a petitioner must establish in order to meet this standard: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1322.

To satisfy the first prong of *Althen*, a petitioner must show that it is more likely than not that the vaccine received *can* cause the type of injury alleged. *See Pafford v. Sec'y of HHS*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). The supporting medical theory set forth by a petitioner need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). At the same time, the theory cannot be baseless or completely speculative; it must be informed by "sound and reliable medical or scientific explanation." *Id*. at 548. The undersigned may also deem an opinion or theory unreliable where "'there is simply too great an analytical gap between the data and the opinion proffered.'" *Cedillo v. Sec'y of HHS*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (quoting *Joiner*, 522 U.S. at 146); *see also Caves v. Sec'y of HHS*, 100 Fed. Cl. 119, 136 (2011) (holding that Special Master did not err in deeming expert's theory unreliable where theory and its conclusions "were too far removed from the other evidence" in the case).

While the first prong of *Althen* focuses on general causation, that is, the second prong focuses on specific causation, that is, whether the administered vaccine *actually* caused the injury. *See Pafford*, 451 F.3d at 1355-56. To meet *Althen*'s second prong, a petitioner must establish "a

logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Id*. at 1355 (internal quotation marks omitted). Of note, the temporal proximity between the vaccination and the claimed injury is a factor to be considered under *Althen*'s second prong; however, temporal association alone is insufficient to satisfy that prong. *Wirt v. Sec'y of HHS*, No. 11-118V, 2014 U.S. Claims LEXIS 348, at *35 (Fed. Cl. Spec. Mstr. Apr. 18, 2014); *see Grant v. Sec'y of HHS*, 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("[A] proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury."). To fulfill her burden, a petitioner may present circumstantial evidence and reliable medical opinions; she is not required to offer "epidemiologic studies, rechallenge, presence of pathological markers or genetic disposition, or general acceptance in the scientific and medical communities" to establish a logical sequence of cause and effect. *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1322 (Fed. Cir. 2006).

Under *Althen*'s third prong, a petitioner must produce preponderant evidence of "a proximate temporal relationship between vaccination and injury." *Pafford*, 451 F.3d at 1356. This prong helps to establish the connection between the causal theory of Prong One and the more fact-based cause and effect arguments of Prong Two by demonstrating "that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of HHS*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

B. Arguments Presented

In their post-hearing memoranda, Petitioner and Respondent posit that four principal disputes remain in the case: whether Petitioner (1) showed that K.T. has epileptic encephalopathy ("EE"), as well as MAE; (2) provided a plausible, reliable, and persuasive medical theory causally linking the vaccination and Petitioner's injury; (3) demonstrated a logical sequence of cause and effect between the vaccine and her injury; and (4) alleged a medically appropriate temporal association between the administration of the vaccine and the first symptom of her injury. *See* Pet'r's Post H'rg Mem. at 13-19, ECF No. 73; Resp't's Post H'rg Br. at 2-9, ECF No. 74.

i. Diagnosis

Petitioner and Respondent agree that (a) Petitioner suffers from MAE, (b) MAE generally is categorized as a form of EE, and (c) not all individuals with MAE also have EE. *Compare*

Pet'r's Post Hr'g Mem. at 13-15 *with* Resp't' Post Hr'g Br. at 2-3.[6] But in applying (c) to Petitioner's case, the parties diverge.

Petitioner argues that a diagnosis of EE requires *either* a "regression *or* a plateau" in cognitive or behavioral development, and that Petitioner's development plateaued after the vaccination, and she therefore qualifies for EE. Pet'r's Post Hr'g Mem. at 13-14. Dr. Shafrir posits that K.T. displayed "obvious encephalopathic symptoms" indicative of EE. Tr. at 110. Dr. Shafrir points out that prior to the vaccination, K.T.'s medical records indicated that K.T. had "met all her developmental milestones," and was "cruising currently" and "very verbal." *Id.* at 83 (internal quotation marks omitted). After the vaccination, while admitting that K.T. did not seem to suffer "regression," Dr. Shafrir believes that the records document "stagnation of her development." *Id.* at 84. In particular, Dr. Shafrir draws attention to K.T.'s individualized education program, which noted "an IQ of 77" and "expressive language percentile below 1 percent," as well as her mother's description of motor and coordination problems. *Id.*

By contrast, Respondent contends that a mere plateau in development is insufficient to constitute EE; rather, Dr. Holmes attests, doctors must observe regression in order to diagnose EE, and Petitioner's medical records demonstrate no such regression. Resp't's Post Hr'g Br. at 2-3. Dr. Holmes also notes that none of K.T.'s treating physicians indicated that she had EE. Resp't's Ex. L at 3. Dr. Holmes further posits that the medical records suggested that K.T. had progressed since August 2009. Tr. at 172-75. Far from a decrease in function, Dr. Holmes suggests that K.T.'s "speech abnormality appears to be confined to an articulation problem," and it "would be highly unlikely [EE] would cause such a localized deficit." Resp't's Ex. L at 4. In the absence of regression, Dr. Holmes concludes, one could not find that K.T. had EE.

ii. *Althen* Prong One

Petitioner, via Dr. Shafrir, generally theorizes that the MMR vaccine could cause MAE via an adverse immunological response. Tr. at 94. Dr. Shafrir proposes three potential responses, any of which could be sufficient to cause MAE: molecular mimicry, bystander activation, and epitope spread. *Id.* at 127-28.

Of these, Dr. Shafrir mostly discusses molecular mimicry. *See id.* at 94-103, 127-30. To outline this theory, Dr. Shafrir cites Tishler & Shoenfeld, who explain that molecular mimicry

[6] Petitioner's position on (c) is relatively unclear, given that Dr. Shafrir seems to contradict Petitioner's assertion in her closing brief, when he opined at the hearing that MAE is a form of EE. Tr. at 75 (citing Pet'r's Ex. 39, ECF No. 54-2 (Sarah A. Kelley & Eric H. Kossoff, *Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress*, 52 Developmental Med. & Child Neurology 988 (2010))). Whatever Petitioner's position, it is immaterial, as will become clear later in this decision.

refers to the process by which "antigenic determinants of [an infectious agent's] microorganisms are recognized by the host's immune system as similar to its own antigenic determinants and, because of the structural resemblance, antibodies and autoreactive T cells not only destroy the invading pathogen but can react with host tissues as well." Pet'r's Ex. 46 at 3, ECF No. 54-9 (citation omitted) (Moshe Tishler & Yehuda Shoenfeld, *Vaccines & Autoimmunity*, The Autoimmune Diseases 309 (Noel R. Rose & Ian R. Mackay eds., 2006)) (hereinafter "Tishler & Shoenfeld" with pincites to Petitioner's pagination).

As an example of this reaction, Tishler and Shoenfeld cite the development of Guillain-Barré syndrome ("GBS"), which is often preceded by Campylobacter jejuni infection. *Id.* Of note, they point out that the bacterium that is responsible for the infection "expresses a lipolyscharide molecule that mimics various gangliosides presented in high concentration in peripheral nerves"; and, sera taken from GBS patients in the acute phase of the disease exhibits antibodies against Gangliosides. *Id.* Importantly, they continue, "the specificity of these antiganglioside antibodies is closely related to [both] the nature of the infection preceding GBS . . . and the pattern of clinical features in these patients." *Id.*

In other words, Dr. Shafrir contends, after receiving the MMR vaccine, K.T.'s immune system potentially failed to distinguish the antigenic determinants of the virus present in the vaccine from K.T.'s own cells. Pet'r's Ex. 38 at 4-5. As a result, the immune system's antibodies and autoreactive T cells destroyed the tissues of both the vaccine antigens and of K.T. herself. *Id.*

More specifically, Dr. Shafrir argues that recent evidence suggests that antibodies to contactin-associated protein-like 2, also known as "Caspr2," could have caused K.T.'s MAE when they were created by her immune system in response to the MMR vaccine. *Id.* at 6; *see* Tr. at 100 (stating that "appearance of antibodies against Caspr2 could be the cause of the onset of her epileptic encephalopathy"). In support, Dr. Shafrir points to a study by Obregon et al. *See* Pet'r's Ex. 38 at 6 (citing Pet'r's Ex. 45 at 3-6, ECF No. 54-8 (Demian F. Obregon et al., *Potential Autoepitoope within the Extracellular Region of Contactin-Associated Protein-like 2 in Mice*, 4 British J. Med. & Med. R. 416 (2014)) (hereinafter "Obregon et al." with pincites to Petitioner's pagination)).

In Obregon et al., researchers obtained sera from 26 children with autism and 18 children without autism and screened the sera for the presence of antibodies against peptide targets of Caspr2 bearing similar sequences to those peptides in known human pathogens. Obregon et al. at 7. The researchers observed that the sera from the children with autism exhibited comparatively elevated levels of antibody binding to two sequences of Caspr2, one of which is present in the pertussis virus and another which is present in the large protein of the measles

virus. *Id.* at 4-5, 7. Thereafter, the researchers obtained 48 mice[7] and injected them with either lipopolysaccharide ("LPS"), an endotoxin that produces a strong response from normal animal immune systems, *see* Sayaka Iizasa et al., Arabidopsis *LBP/BPI related-1 and -2 bind to LPS directly and regulate* PR1 *expression*, 6 Scientific Reports, no. 27527, June 8, 2016, at 1, or phosphate buffered saline. *Id.* They subsequently immunized the mice with either (1) a pathogen peptide containing the sequence of Caspr2 found in the pertussis virus and implicated in the elevated binding of antibodies in the sera from children with autism, or (2) a control peptide, which contained a sequence of Caspr2 not believed to bear any similarity with known human bacterial or viral pathogen proteins. *Id.* at 8. After the immunizations, the researchers conducted motor function testing and found that only those mice both pretreated with LPS and immunized with the pathogen peptide expressed "significantly elevated levels of antibodies able to bind" to the peptide containing the Caspr2 sequence. *Id.*

Accordingly, Obregon et al. concluded that Caspr2 "contains a potential autoepitode within the extracellular region." *Id.* at 13. That being said, the researchers were careful to note the study's limitations:

> Importantly, the results have significant limitations including that a synthetic linear peptide representing a small fragment of [Caspr2], not in its native form, was used to immunize and evaluate the effects of the [Caspr2 sequence-similar region] in mice and detect [Caspr2 sequence similar region]-binding antibodies in human samples. Although the antibodies binding to [the Caspr2 sequence similar region] generated by LPS and [pathogen peptide] pretreatment appeared to bind [Caspr2] in its native form on neuronal cells . . . , it remains to be determined whether the extracellular region of [Caspr2] analogous to the [pathogen peptide] would be available for antibody binding in its native conformation in humans. Further, the human sample data contained within the present study is significantly limited by the small sample size and dissimilarity between groups as well as the lack of or incomplete medical histories. Further complete immunological characterization of the evaluated mice was not completed prior or after LPS or [pathogen peptide] treatment.

Id.

[7] Although the study claims the use of 54 mice, it notes "n=8, 4 [female]/4 [male] per group, 6 groups," which suggests the use of 48 mice. *Id.* at 5. Because it is impossible to create either 6 groups from 54 mice that would result in an even distribution of males and females or 4 evenly distributed test groups (which the study claims that it did), the undersigned presumes that this is a misprint. *Id.*

Dr. Shafrir admits yet another limitation specific to this case: Obregon et al. involved autism, not epilepsy; nevertheless, he asserts that Obregon et al. is "very relevant" to K.T.'s condition, Tr. at 94-95, given that antibodies to Caspr2 "were implicated in" autoimmune epilepsy, autoimmune encephalitis, and epilepsy and developmental regression," Pet'r's Ex. 38 at 6. To support this assertion, he cites three studies. *Id.* The first observed improvements following immunotherapy in one individual with adult onset epilepsy, who was positive for Caspr2 antibodies. Pet'r's Ex. 53 at 3-4, ECF No. 55-7 (James B. Lilleker et al., *VGKC complex antibodies in epilepsy: Diagnostic yield and therapeutic implications*, 22 Seizure 776 (2013)). The second tested patients with autoimmune encephalitis, noting that Caspr2 was generally associated with peripheral motor excitability. Pet'r's Ex. 54 at 1, ECF No. 55-8 (Christopher J. Klein et al., *Insights From LGI1 and CASPR2 Potassium Channel Complex Autoantibody Subtyping*, 70 JAMA Neurology 229 (Feb. 2013)). The final study found a homozygous mutation of Caspr2 in Old Order Amish Children with cortical dysplasia, focal epilepsy, relative macrocephaly, and diminished deep-tendon reflexes. Pet'r's Ex. 55 at 1, ECF No. 55-9 (Kevin A. Strauss et al., *Recessive Symptomatic Focal Epilepsy and Mutant Contactin-Associated Protein-like 2*, 354 New England J. Med. 1374 (2006)). Taken together, Dr. Shafrir posits, these and the aforementioned studies permit him to "present a well-founded mechanism by which the MMR vaccine caused [K.T.'s] symptoms by induction of autoimmune response to one or more of the protein [sic] by the measles, mumps, and rubella viruses through a mechanism of molecular mimicry." Pet'r's Ex. 38 at 6.

Respondent argues that Petitioner's theory of causation is unpersuasive. Respondent counters that Obergon et al.'s "relevance to [K.T.]'s case is minimal." Resp't's Post Hr'g Mem. at 4. Initially, Dr. Holmes testified that the study created "a very artificial situation that doesn't reflect what happened to [K.T.] one bit," by giving "LPS, which kind of destroys the brain," to the mice before they found an increase in autoantibodies." Tr. at 187. Dr. Holmes also points out two other significant limitations: (1) the study dealt with autism, not MAE, and (2) the study focused on the pertussis virus, which is not a component of the MMR vaccination. *Id.* In his supplemental expert report, Dr. Holmes adds that it is "highly unlikely that an autoimmune process would target speech articulation without impairing other neurological function." Resp't's Ex. L at 3. With these limitations, Dr. Holmes explains, "it's a huge jump to look at [Obergon et al.] and say MAE is caused by autoantibodies," Tr. at 227; indeed, he continued, such a theory is not one generally discussed by pediatric neurologists, *id.* at 188. In sum, Dr. Holmes knew "of no convincing evidence whatsoever" to suggest that MMR could cause epilepsy or MAE. *Id.* at 188.

While Respondent acknowledges that Petitioner nominally presented bystander activation and epitope spreading as potential theories of causation, she asserts that these were mentioned

only sparingly, and that Petitioner's focus was almost wholly on molecular mimicry. Pet'r's Post Hr'g Mem. at 5. These alleged links, Respondent claims, are entirely speculative. *Id.*

In addition to the specific evidence related to mechanism, Petitioner posits that there are global studies linking the MMR vaccination and K.T.'s injury. *See* Pet'r's Ex. 16 at 16-19. Dr. Shafrir cites a comprehensive study, commonly known as the NCES study, which found a "statistically significant association . . . between onset of acute neurological illness and measles immunization given 7-14 days before onset of illness in cases compared with controls." *Id.* at 16-17 (quoting Pet'r's Ex. 18, ECF No. 36-2 (R. Alderslade et al., *The National Childhood Encephalopathy Study: A Report on 1000 Cases of Serious Neurological Disorders in Infants and Young Children from the NCES Research Team, in* Whooping Cough: Reports from the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation, at 149 (U.K. Dep't of Health & Social Security ed., 1981))) (emphasis omitted). Dr. Shafrir also points to a series of studies showing abnormal EEGs after the measles infection or measles vaccination. Pet'r's Ex. 16 at 17-19 (citing Pet'r's Ex. 20, ECF No. 36-5 (G. Pampiglione et al., *Transient Cerebral Changes After Vaccination Against Measles*, The Lancet 5 (July 3, 1971)); Pet'r's Ex. 21, ECF No. 36-6 (G. Pampiglione, *Prodromal Phase of Measles: Some Neurophysiological Studies*, 2 British Med. J. 1296 (1964)); Pet'r's Ex. 22, ECF No. 36-7 (Frederic A. Gibbs & Ira M. Rosenthal, *Electroencephalography in Natural and Attenuated Measles*, 103 Am. J. of Diseases of Children 395 (Mar. 1962)); Pet'r's Ex. 23, ECF No. 36-8 (Frederic A. Gibbs et al., *Electroencephalographic Abnormality in 'Uncomplicated' Childhood Diseases*, 171 J. Am. Med. Ass'n 1050 (Oct. 1959))). Finally, Dr. Shafrir notes a case study in which a child developed Lennox-Gastaut syndrome, a form of EE, on the fourteenth day following a measles vaccination. Pet'r's Ex. 16 at 19 (citing Pet'r's Ex. 24, ECF No. 36-9 (Tatsuya Ishikawa et al., *Lennox-Gastaut syndrome after a further attenuated live measles vaccination*, 21 Brain & Development 563 (1999))).

Dr. Holmes responds that the "studies cited by Dr. Shafrir deal with very small populations and do not have sufficient power to result in any type of meaningful conclusions." Resp't's Ex. A at 6. As to the NCES study, Dr. Holmes observes that it studied five different diagnoses, none of which apply to K.T. *Id.* at 5-6. As to the EEG studies, Dr. Holmes contends that all such changes disappeared after the fourteenth day following the vaccination in the EEG study, and that the Gibbs & Rosenthal study dealt with the measles infection, not the vaccination. *Id.* at 6. Similarly, Dr. Holmes sees no relevance in a case study, like Ishikawa et al., that examines a condition, Lennox-Gastaut syndrome, which does not afflict K.T. *Id.*

iii. *Althen* Prongs Two and Three

In his initial expert report, Dr. Shafrir claims that one could say "within reasonable degree of medical certainty," that K.T.'s EE was the result of the MMR vaccine, but offers little beyond temporal proximity to create a logical sequence of cause and effect linking the vaccine and the injury. Pet'r's Ex. 16 at 17-19. At hearing, Dr. Shafrir discussed *Althen*'s second prong only sparingly:

> So, [K.T.] had – was born with a genetic propensity for Doose Syndrome and she developed Doose syndrome after she received the MMR vaccination. During the acute phase of the vaccine-induced infection, antibodies against the vaccine components produced the last environmental – or the last hit that, on top of her genetic propensity, tipped her into developing Doose syndrome with all its unfortunate consequences.

Tr. at 102-03.

Respondent counters that none of K.T.'s treating physicians opined or suggested that the MMR vaccination was the underlying cause of any of her adverse health conditions. *Id.* at 7-8. Indeed, Respondent observes, Dr. Gibbons specifically found no evidence implicating issues with vaccination. *Id.*

Furthermore, Respondent contends, it was K.T.'s April 2009 seizure, not the first seizure after the MMR vaccination, which represented the onset of her MAE. Resp't's Post Hr'g Mem. at 7-8. This position, Respondent continues, is supported by both Dr. Holmes and Dr. Facchini, the treating physician. *Id.* at 7. On this point, Dr. Holmes argues that K.T.'s development of MAE was not temporally consistent with a finding of causation because "the clinical course of [K.T.] indicates she has epilepsy that likely began before the MMR was administered as evidenced by the febrile seizure." Resp't's Ex. A at 5. In support, Dr. Holmes notes that fever precipitated K.T.'s first seizure in April 2009, which is typical for children of epilepsy. *Id.* In his supplemental report, Dr. Holmes explains that it "is now widely recognized that febrile seizures are frequently the first seizure type at the onset of epilepsy." Resp't's Ex. L at 2. At the same time, Dr. Holmes admitted that "it is possible" that K.T.'s April 2009 seizure was benign and unrelated to MAE. Resp't's Ex. A at 5.

Dr. Shafrir is "surprised" at Respondent's claim that the first symptom of K.T.'s MAE was her febrile seizure in April 2009. Tr. at 88. Dr. Shafrir emphasizes that the later seizures were "completely different," as they featured characteristics like "eye rolling upwards, dropped arms, and behavioral arrest with unresponsiveness lasting less than a minute," none of which presented in her April 2009 seizure. Pet'r's Ex. 38 at 1. Moreover, Dr. Shafrir asserts, febrile seizures are commonplace, and neurologists are taught to inform patients that the seizure causes

neither epilepsy nor cognitive problems. *Id.* In support, Dr. Shafrir cites medical literature, which provides that "'children with simple febrile seizure ha[ve] approximately the same risk of developing epilepsy by age seven as does the general population.'" *Id.* at 90 (quoting Pet'r's Ex. 61 at 2, ECF No. 67-4 (Am. Academy of Pediatrics, Steering Comm. on Quality Improvement & Mgmt., Subcommittee on Febrile Seizures, *Febrile Seizures: Clinical Practice Guideline for the Long-term Mgmt. of the Child With Simple Febrile Seizures*, 121 Pediatrics 1281 (2008))). Dr. Shafrir admits that a large number of patients with MAE have a history of febrile seizures, *id.* at 133-34; still, he cautions that this in no way buttresses the theory that K.T.'s febrile seizure was related to her MAE, *id.* at 250-52. Indeed, he opines that he knows of no case study linking a febrile seizure to the subsequent development of MAE where the incidents were separated by four months of normal health. *Id.* at 251-52.

As to the temporal proximity between the vaccination and the injury, Petitioner uses this as a means to satisfy both *Althen*'s second and third prongs. Dr. Shafrir cites studies showing a clustering of acute encephalopathy on the eighth or ninth day following the MMR vaccination and abnormal EEGs following the measles vaccine, and one case report in which a child developed EE on the fourteenth day following a measles vaccination. Pet'r's Ex. 16 at 17-19. Petitioner also attempts to use her evidence of a temporal association between the vaccination and the injury in order to meet her burden under *Althen's* second prong. As to that alleged association, Dr. Shafrir claims that the timing of the development of MAE was consistent with both the NCES study and the vaccine injury table, which provide for 7 to 14 day and 5 to 15 day onset periods for cases of encephalopathy following the MMR vaccination. Tr. at 103.

For her part, on temporal proximity, in her post-hearing memorandum, Respondent only notes that Dr. Holmes "disagrees with" Dr. Shafrir's conclusion that "'the medical records strongly support temporal relationship between the MMR vaccination and the appearance of seizures and encephalopathy.'" Resp't's Post Hr'g Mem. at 8-9 (quoting Pet'r's Ex. 16 at 20). In the cited portion of his expert report, Dr. Holmes reasserts that K.T. has MAE, not EE, in support of this disagreement. Resp't's Ex. A at 5.

IV. Holding

After reviewing the medical records, expert reports, and arguments of the parties, the undersigned concludes that Petitioner is not entitled to compensation under the Vaccine Act. Although the undersigned concurs with Petitioner's position that K.T. has EE, as well as MAE, the undersigned finds that Petitioner has not established, by a preponderance of the evidence, either a medical theory plausibly linking the MMR vaccination and MAE or sufficient reason to believe that Petitioner's MAE was actually caused by the MMR vaccination.

A. Diagnosis

The undersigned finds that K.T. has EE. Both parties, their experts, and the medical literature agree that a diagnosis of EE "requires demonstration of a failure to develop as expected relative to same-age peers or to regress in abilities." Tr. at 165; *accord* Tr. at 109-10, 234-38. They also agree that K.T., in the words of Dr. Holmes, "failed to develop language as expected from peers." Tr. at 235; *accord* Tr. at 83-84. At this point, it would seem, the undersigned's discussion of this issue should be at an end.

Nevertheless, Respondent and her expert claim, the fact that K.T. did not endure a regression in development makes a diagnosis of EE inappropriate. *See* Tr. at 234-37. Predictably, this led to some bizarre exchanges at the hearing, such as when Dr. Holmes "disagree[d]" that EE could be diagnosed without regression, but admitted that "plateauing of the development" would be sufficient; or, when he agreed that EE "requires either failure to develop as expected relative to same-age peers or to regress," and then, a mere two questions later, argued that the condition of one who "failed to develop as expected relative to same-age peers" would "probably not" qualify as one with EE. Tr. at 234-35. To endorse the position of Respondent and Dr. Holmes would be to endorse logical incongruence—that EE manifests a failure to develop in accordance with one's peers or a regression in development, that K.T. failed to develop in accordance with her peers, but that K.T. does not have EE.

Accordingly, the undersigned finds that Petitioner has demonstrated by a preponderance of the evidence that K.T. has EE.

B. *Althen* Prong One

After considering the literature and report underlying Dr. Shafrir's position, the undersigned finds that Petitioner has not proffered an adequate medical theory causally linking the MMR vaccination and MAE. The analytical gaps between the medical literature and Dr. Shafrir's theory are, in the end, too great and too numerous to persuade the undersigned of the theory's validity.

The undersigned does not doubt the validity of the theory of molecular mimicry, or its potential to explain the adverse effects of vaccines. That being said, Petitioner has not proffered sufficient evidence to believe that the mechanism of molecular mimicry could lead from the MMR vaccination to MAE.

Initially, a significant analytical gap remains in Petitioner's alleged causal chain between vaccination and injury, as Dr. Shafrir presents no specific mechanism to explain why the

corruption of Caspr2 would lead to epilepsy. To clarify the point: in order to explain molecular mimicry, Dr. Shafrir cites the exemplar of GBS and the Campylobacter jejeuni infection, in which the bacterium from the infection expresses a molecule that mimics gangliosides present in high concentration in peripheral nerves, which causes the body's immune system to attack both the infection and the body's own gangliosides. As a result, the patient suffers from peripheral nerve damage. By contrast, in this case, Dr. Shafrir points to studies allegedly showing (a) the existence of molecular mimicry, spurred by a sequence of Caspr2 that is present in viruses that are present in vaccines; and (b) links between the corruption of Caspr2 and epilepsy; however, he offers no biological explanation of how one actually gets from the corruption of Caspr2 to epilepsy. Dr. Holmes points out the causal gap that this lack of explanation creates, as it fails to explain how the autoimmune process would *only* target K.T.'s speech articulation without impairing other long-term neurological function. *Althen* mandates that Petitioner marshal a persuasive medical theory showing how the MMR vaccination could cause MAE, and simply explaining how the theory of molecular mimicry works with other diseases and purporting to show a connection between the MMR vaccination and the disease is insufficient to meet that mandate. In short, Petitioner has alleged that an association exists between a vaccine, a general immune system reaction, and an injury; she has not presented a persuasive causal theory.

Putting the theoretical gap in Petitioner's argument aside, Petitioner has not proffered sufficient evidence to support the association between the MMR vaccine, molecular mimicry, and MAE. All things considered, she presented one probative study of the exact link at issue—Obregon et al. While the undersigned admits, as did Dr. Holmes, that Obregon et al. presents interesting food for thought, it cannot serve as the sole basis to connect the vaccine and the injury in this case.

At the outset, the study itself has limits in its significance, given its study design. There are limited inferences that one can draw from a study of only 48 mice, whose immunological histories were entirely unknown, where only 12 displayed elevated antibody binding. Further, the sera from autistic children used to initially uncover the relevant sequence of Caspr2 for testing has its own limitations due to the small size of the sample and the potentially nonrandom nature of the sample. *See* Obregon et al. at 7 (noting that the children had unknown "pathogen exposure profiles and were "characteristically dissimilar"). Mechanistically, as Dr. Holmes' explained, the study itself created an artificial situation that hardly reflects the natural world—researchers were only able to obtain the relevant results after pretreating the mice with LPS *in addition to* immunizing them with the pathogen peptide. And as to the pathogen peptide tested, it was derived from the sequence of Caspr2 contained in the pertussis virus, not the large protein of the measles virus. To be fair, the sera from autistic children also demonstrated elevated antibody binding to the sequence of Caspr2 contained in the large protein of the measles virus, but it is unclear that the results of Obregon et al. would be reproduced were the latter sequence

used to generate the pathogen peptide. To repeat: this is not to say that the study is unreliable or its results incredible—the undersigned simply points out its limits. Indeed, even the authors of the study go to great lengths to point out the limited inferences that one can draw from its findings. Likewise, the undersigned finds that it is insufficient to serve as the only medical literature purporting to link the MMR vaccination and MAE.

But even if the study were more robust, its use in underlying Petitioner's claim would be problematic because the link between Caspr2 and MAE has not been sufficiently established. Petitioner cites three studies to underscore the link, but none are particularly convincing. The first involves one patient with adult-onset epilepsy, and thus is no more than a case study. The second and third, while studying a larger population, suffer from a different problem—the patients' conditions are quite different from MAE. It is difficult to infer conclusions about MAE and Caspr2 from studies examining autoimmune encephalitis and focal epilepsy in Old Order Amish Children. Because these studies, whether considered in isolation or in concert, cannot show a persuasive link between Caspr2 and MAE, the mere fact that certain sequences of Caspr2 may spur molecular mimicry is of little use to Petitioner.

As for the more general evidence cited by Petitioner and Dr. Shafrir, the undersigned agrees with Dr. Holmes' assessment in his initial report: these studies are largely irrelevant to Petitioner's case, as all deal with conditions that do not afflict K.T. In the absence of the aforementioned findings as to *Althen*'s first prong, these studies might move the needle in Petitioner's favor; but standing alone, these studies cannot support a claim for compensation.

To the extent Petitioner proffers bystander activation and epitope spreading as potential mechanisms by which the MMR vaccination could cause MAE, the undersigned finds them similarly unconvincing. Petitioner cites some evidence which establishes these mechanisms as theories, generally speaking, but nothing showing that they are particularly applicable to the relationship between the MMR vaccine and MAE. For these and the previously mentioned reasons, the undersigned concludes that Petitioner has not met her burden under *Althen*'s first prong.

C. *Althen* Prongs Two and Three

Assuming that Petitioner had met her burden under *Althen*'s first prong, her claim would nevertheless fail because she has not proffered evidence of a logical sequence of cause and effect suggesting that the MMR vaccination caused K.T.'s injury.

That being said, the undersigned disagrees with Respondent's assertion that the main reason for this is because Petitioner's April 2009 seizure, not the first post-vaccination seizure,

represented the onset of her MAE. Her initial seizure was entirely different in kind from the seizures that defined her MAE. Although Respondent is correct that fever often precipitates a child's first epileptic seizure, K.T.'s treating physicians noted that the April 2009 seizure was a febrile seizure following a UTI, not a fever. In any event, Petitioner had a fever only a few days before her first seizure following the vaccination, so it is at least equally possible that it is that seizure which was her first. While febrile seizures occasionally precede MAE, they typically do so within weeks, not *four months*. The undersigned recognizes that Dr. Facchini agreed with Dr. Holmes' ultimate opinion on this matter; nonetheless, the treating physician's impression is but one of many factors to be considered in judging the time of onset. On balance, the undersigned concludes that K.T.'s MAE began nine days after the MMR vaccination.

Even so, Petitioner still must establish a logical sequence of cause and effect leading from vaccine to injury in K.T.'s case, and the record reveals no such sequence. At the outset, none of K.T.'s treating physicians linked her vaccination and injury. Dr. Voss's letter advising against future vaccines is, at best, offset by Dr. Gibbons's statements opining against causation. As is reproduced above, Dr. Shafrir hardly discussed *Althen*'s second prong at the hearing. To the extent he did, he merely restated his theory of causation and inserted K.T.'s name. In the end, all that remains to support *Althen*'s second prong is the temporal proximity between the vaccination and K.T.'s first seizure, and temporal proximity alone cannot satisfy *Althen*'s second prong, or the distinction between prongs two and three would be meaningless.

To be sure, Respondent has offered little upon which to find in her favor with respect to *Althen*'s second prong (aside from the previously rejected notion that the April 2009 seizure represented the onset of K.T.'s condition). Regardless, it is Petitioner, not Respondent, who must prove, by a preponderance of the evidence, that the MMR vaccination actually caused K.T. to develop MAE. Petitioner has not met that burden.

Although immaterial to the ultimate disposition in this case, the undersigned finds that Petitioner satisfied her burden as to *Althen*'s third prong. Petitioner presented evidence, from the NCES study and the vaccine table, of an onset period matching that observed in K.T.'s medical history. Respondent refuted Petitioner's prong three evidence only indirectly, by arguing that K.T. did not have EE and that the first manifestation of K.T.'s MAE occurred when she suffered from the febrile seizure in April 2009. Because Respondent's arguments on these grounds are unpersuasive and Respondent presents no other reason to reject Petitioner's claim of temporal proximity, the undersigned concludes that Petitioner has met her burden under *Althen*'s third prong.

V. Conclusion

The undersigned is sympathetic to K.T.'s ordeal; however, for the aforementioned reasons, the undersigned concludes that Petitioner has not shown, by a preponderance of the evidence, that the MMR Vaccine caused her injuries. Therefore, she is not entitled to compensation under the program. [8]

IT IS SO ORDERED.

s/Lisa Hamilton-Fieldman
Lisa Hamilton-Fieldman
Special Master

[8] Pursuant to Vaccine Rule 11(a), the parties can expedite entry of judgment by filing a notice renouncing the right to seek review by a United States Court of Federal Claims judge.